

Please substitute the following paragraph for the third paragraph on page 3 of the specification.

Page 3, third paragraph (AMENDED)

Methods of optical resolution ~~includes~~ include *per se* known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes *per se* known ~~method~~ methods.

Please substitute the following paragraph for the second paragraph on page 4 of the specification.

Page 4, second paragraph (AMENDED)

The “diastereomer method” includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said “optically active reagent” includes, for example, ~~an~~ optically active organic acids such as MTPA [ $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid] and (-)-menthoxyacetic acid; and ~~an~~ optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane, etc.

Please substitute the following paragraph for the fifth paragraph on page 4 of the specification.

Page 4, fifth paragraph (AMENDED)

Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in ~~mixture~~ mixtures of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100).

Please substitute the following paragraph for the fifth paragraph on page 5 of the specification.

Page 5, paragraph 5 (Once Amended)

~~Thus~~ A thus-obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing

the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes ~~more-unlikely~~ less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low ~~doses~~ dosage and with a low prevalence of adverse reactions.

Please substitute the following paragraph for the second paragraph on page 6 of the specification.

Page 6, paragraph 2 (Once Amended)

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive ~~burn~~ burns necessitating intensive treatment); treatment and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration etc.

Please substitute the following paragraph for the eighth paragraph on page 10 of the specification.

Page 10, eighth paragraph (AMENDED)

For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers (e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), ~~Polykid~~ Polyquid PA30 (trade name; produced by San-yo Chemical)), carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers (e.g., Eudragit NE30 D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.); water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, ~~triacetine~~ triacetin and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar

alcohols (e.g., sorbitol, mannitol, ~~multitol~~ maltitol, reduced starch saccharides, xylitol, reduced ~~paratinose~~ palatinose, erythritol, etc.), crystalline cellulose (e.g., Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium)), low-substituted hydroxypropyl cellulose (e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof); binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

Please substitute the following paragraph for the fourth paragraph on page 14 of the specification.

Page 14, fourth paragraph (AMENDED)

Lansoprazole (racemate) (34.2 g) was dissolved in 2-propanol (1,710 ml) and hexane (1,140 ml) containing triethylamine (0.2%) and fractionated by HPLC (column: CHIRALCEL OD 50 mm dia. X 500 mm, temperature: room temperature, mobile phase: hexane/2-propanol = 85/15, flow rate: 60 ml/min, detection wavelength: 285 nm, ~~(1-shot)~~ single injection: about 300 mg) to isolate the individual optical isomers. Fractions of an optical isomer of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol (250 ml); after triethylamine (3 ml) was added, the solution was filtered through a 0.45 µm filter. After the filtrate was concentrated, hexane was added, and the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (9.31 g, optical purity 98.3%ee) as an amorphous substance.

Please substitute the following paragraph for the second paragraph on page 26 of the specification.

Page 26, paragraph 2 (Once Amended)

#### INDUSTRIAL APPLICABILITY

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid ~~secretion-inhibit~~ secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher C<sub>max</sub> and a greater AUC than the racemate, and becomes ~~more-unlikely~~ less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low ~~doses~~ dosage and with a low prevalence of adverse reactions.